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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/218,660	12/22/1998	EVAN C. UNGER		2775

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DLA PIPER US LLP
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EXAMINER	
SOROUSH, LAYLA	
ART UNIT	PAPER NUMBER
1617	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/19/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/218,660	UNGER ET AL.	
	Examiner	Art Unit	
	Layla Soroush	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *100,102,127,194-200,203 and 210-213,217-228, 294-300, 303, 310-329, 331-337, 347-356, 412* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date ~~9/7/04~~. 9/27/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 25, 2006 has been entered. Claims 100, 102, 127, 194-200, 203, 210-213, 217-228, 294-300, 303, 310-329, 331-337, 347-356, and 412 are pending.

Priority

The effective priority date used for examination of the instant application is May 1, 1996. The applicant's arguments towards the effective priority date of the present application have been taken into consideration but are not found persuasive for the reasoning's stated in the office action mailed on December 28, 2005.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 100, 102, 127, 194-200,203, 210-213, 217-220,294-300, 303, 310-317, 326, 412 are rejected under 35 U.S.C. 103(a)as being unpatentable over Allen US Patent 5,620,689 (Allen) in view of Wallach US Patent 4,853,228 (Wallach), Schneider US Patent 5,643,553 (Schneider) and Porter US Patent 5,648,098 (Porter).

The instant claims are directed toward methods of use and formulation comprising targeted phospholipid containing vesicles comprising a substantially insoluble gas, a linking group and a targeting ligand, wherein the linking group is a hydrophilic polymer that is covalently bound to both the surface of the lipid vesicle and said targeting ligand and is selected from a group consisting of PEG, polypropylene glycol, polyvinylalcohol. PVP, and copolymers thereof and wherein the vesicle is free of disulfide linkage.

Allen discloses methods of treating patients with targeted liposomes. (abstract, col 29, lines 2-30). Allen's composition comprising lipid vesicles such as liposomes which are used for delivery of diagnostic or therapeutic agents. Allen discloses that the liposomes shells maybe formed from a phospholipid such as PE, (see entire bol 6-8). Attached to the vesicle shell is a polymer chain of PEG having a molelular weight org between 500-10000 dalton which is attached covalently to an antibody (see col 2, lines 55-66; col 5-6; fig. 1, col 11, lines 38-66; col 12, lines 29-34). Allen's liposomes contain entrapped therapeutic agents and imaging agents (see col 7, lines 30-55).

Allen does not teach gas-containing vesicles.

Wallach's teachings are complementary to Allen's as it explicitly describes the covalent bonding between the linker, targeting agent and the phospholipids moiety of a liposomal shell. Wallach discloses a composition comprising lipid vesicles such as liposomes for delivery of contrast agents and therapeutic agents (see col 5, lines 8-30; col 10, lines 10-42). Wallach teaches that his lipid vesicles can be conjugated to targeting ligands such as peptides to provide the advantage of in vivo site specificity (see col 4, lines 61+). Wallach's compositions comprise a lipid bilayer vesicles having a targeting moiety and a polymeric surfactant. (see col 9, lines 10-36). Wallach specifically teaches that the targeting ligand may be conjugated to the microspheres by covalent attachment of the targeting molecule to the amino group of PE via a spacer group of polyoxyethylene head groups, (see col 5, lines 1-7). The vesicles of Wallach do not contain a disulfide linkage. Wallach only fails teach liposome containing a gaseous ultrasound contrast agent. The use of gaseous perfluorocarbons in combination with drug delivery vesicles has been well established in the art. Schneider for example teaches liposomal composition comprising gas-filled microbubbles, wherein the microbubbles may contain various surfactant such as a microbubble shell forming phospholipid or more specifically PE, as well as, polymeric surfactants, such as PEG surfactants, (col 6, lines 25-64; claims 4-20).

Schneider also teaches that targeting ligands (e.g, polypeptides, antibodies, etc..) may be bounded by the stabilizing surfactant layer of the microbubbles to provide site-specific targeting of the diagnostic or therapeutic microbubbles (see col 9, lines 10 +, example 11). Thus, Schneider teaches

microbubbles that comprise PE shells combined with a PEG surfactant, which maybe bound with a peptide targeting ligand.

Schneider does not explicitly teach a perfluorinated gaseous liposome that is covalently bound to a targeting ligand via a PEG linker.

However, Porter teaches method of improving drug activity when microvesicles contains perfluorocarbon gas, which cavitate in the presence of an ultrasound field. (see abstract; col 8, lines 19-45). Porter specifically exemplify perfluorobutane as a suitable gas. (see col 8, lines 38-42).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of invention to further incorporate a gaseous ultrasound contrast agent of Schneider in the liposomes of Allen and Wallach and use such formulations for therapeutic or diagnostic purposes, because as suggested by both Allen and Wallach, the liposomes can contain a contrast agent. Further, the ordinary skill in the art would have had a reasonable expectation of success to use a perfluorcarbon gaseous contrast agents in the liposomes of Wallach and Allen, because as taught by Schneider and Porter, gaseous vesicles, specifically perflourocarbon gases such as perfluorobutane, improve drug delivery of a therapeutic agent to a site of interest.

Claims 318-325, 327-329, 331-337, 347-356 are rejected under 35 U.S.C. 103(a) as being unpatentable over Allen in view of Wallech, Schneider and Porter as applied to claims 100, 102, 127, 194-200, 203, 210-213,217-220, 294-300,303, 310-317, 326, 412 and further in view of Ginsburg US Patent 5,656,442 (Ginsburg).

The combination of Allen, Wallach, Schneider and Porter are described above. Such combination does not teach the specific targeting group of Arg-Gly-Asp ("RGD") or Lys-Gln-Ala-Gly-Asp-Val.

Ginsburg discloses the synthetic alpha-amino acid containing chains of Lys-Gln- Ala-Gly-Asp-Val or RGD (col 33, lines 45-55). Ginsburg further teaches that such amino-acid chains specifically bind to fibrinogen of the platelet membrane glycoprotein complex lib/IIia receptor and that they can be used as a targeting ligand in an in vitro kit (abstract). Although the combination of the teachings of Allen, Wallach, Schneider and Porter does not specifically teach the use of Lys-Gln-Ala-Gly-Asp-Val or RGD as a targeting agent, they suggest the use of any suitable targeting agent to improve specificity of their drug delivery system. Accordingly, it would have been obvious to one of ordinary skill in the art at the time of invention to use a suitable targeting agent such as those taught by Ginsburg, because the ordinary artisan would have had a reasonable expectation of success to improve specificity of a drug delivery vesicles to platelet membranes when employing Ginsburgs' targeting agents.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686

F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 100 is rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-58 of U.S. Patent No. 6,521,211. Although the conflicting claims are not identical, they are not patentably distinct from each other because they overlap in scope. The instant pending claims are directed to a formulation for therapeutic or diagnostic use comprising targeted gas-filled vesicles which comprise one or more membranes defining an internal void that contains a substantially insoluble substance, the substance being in a gaseous form at ambient conditions, the substance selected from the group consisting of perfluorocarbons and sulfur hexafluoride, said membrane comprising a phospholipid, and being free of disulfide linkages, and further comprising a lipid covalently conjugated to a targeting ligand via a linking group, wherein[[:]] said linking group is a hydrophilic polymer selected from the group consisting of polyethylene glycol (PEG), pol~ropylene glycol, pol~inylalcohol, polyvinylpyrrolidone, and copolymers thereof, and wherein said targeting ligand is selected from the group consisting of proteins, peptides, saccharides, steroids, steroid analogs, bioactive agents and genetic material." The patented claims are directed to the same process steps but they are directed

to diagnostic methods of ultrasound. The only difference between the patented claims and the pending claims are in the recitation of their intended use. However, since the patented claim meets all the elemental steps of the instant pending claim, they inherently are capable of performing the same intended use as instant claims. Accordingly, it would have been obvious to one of ordinary skill in the art at the time of invention to practice the scope of the instant claims once in possession of the patented claims.

Claims 100, 194-200 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 73, 76,101-112 of copending Application No. 10/341167. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant pending claims are directed to a formulation for therapeutic or diagnostic use comprising targeted gas-filled vesicles which comprise one or more membranes defining an internal void that contains a substantially insoluble substance, the substance being in a gaseous form at ambient conditions, the substance selected from the group consisting of perfluorocarbons and sulfur hexafluoride, said membrane comprising a phospholipid, and being free of disulfide linkages, and further comprising a lipid covalently conjugated to a targeting ligand via a linking group, wherein[[:]] said linking group is a hydrophilic polymer selected from the group consisting of polyethylene glycol (PEG), pol~ropylene glycol, pol~inylalcohol, polyvinylpyrrolidone, and copolymers thereof, and wherein said targeting ligand is selected from the group consisting of proteins, peptides, saccharides, steroids, steroid analogs, bioactive agents and

genetic material" whereas the co-pending claims are directed to therapeutic methods of ultrasound comprising administering to a patient a lipid vesicle encapsulatic a gas and exposint the patient to two subsequent ultrasound frequencies. The only difference between the copending claims and the pending claims of the instant application is in the recitation of their intended use. However, since the copending claims meet all the elemental steps of the instant pending claim, they inherently are capable of performing the same intended use as instant claims. Accordingly, it would have been obvious to one of ordinary skill in the art at the time of invention to practice the scope of the instant claims once in possession of the patented claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

Applicant's arguments filed August 25, 2006 have been fully considered but they are not persuasive.

Applicant argues that Porter is not a competent prior art because it has an effective filing date that is after the instant application. However, for the reasons set forth in the records (see office action mailed on December 28, 2005) the above priority date of the instant case is May 1, 1996. The Examiner maintains the rejection.

Applicant's arguments with respect to this rejection have been fully considered but are not found persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091,231 USPQ 375 (Fed. Cir. 1986). Here, the combined teachings of the cited references meet the limitations of the instant claims. Therefore, the rejection is proper.

Applicant's arguments that none of the references teach or motivate one skilled in the art to prepare a perfluorinated gaseous liposome that is covalently bound to a targeting ligand via a PEG linker is not persuasive. In reply, Examiner respectfully restates that "Porter teaches method of improving drug activity when microvesicles contains perfluorocarbon gas, which cavitate in the presence of an ultrasound field. (see abstract; col 8, lines 19-45). Porter specifically exemplify perfluorobutane as a suitable gas. (see col 8, lines 38-42).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of invention to further incorporate a gaseous ultrasound contrast agent of Schneider in the liposomes of Allen and Wallach and use such formulations for therapeutic or diagnostic purposes, because as suggested by both Allen and Wallach, the liposomes can contain a contrast agent. Further, the ordinary skill in the art would have had a reasonable expectation of success to use a perfluorcarbon gaseous contrast agents in the liposomes of Wallach and Allen, because as taught by Schneider and Porter, gaseous vesicles, specifically

perflourocarbon gases such as perfluorobutane, improve drug delivery of a therapeutic agent to a site of interest."

Additionally, "Wallach's teachings are complementary to Allen's as it explicitly describes the covalent bonding between the linker, targeting agent and the phospholipids moiety of a liposomal shell. (see col 5, lines 8-30; col 10, lines 10-42; col 4, lines 61+; col 9, lines 10-36). Wallach specifically teaches that the targeting ligand may be conjugated to the microspheres by covalent attachment of the targeting molecule to the amino group of PE via a spacer group of polyoxyethylene head groups, (see col 5, lines 1-7). The vesicles of Wallach do not contain a disulfide linkage. 19. Thus, it would have been obvious to one of ordinary skill in the art at the time of invention to further incorporate a gaseous ultrasound contrast agent of Schneider in the liposomes of Allen and Wallach and use such formulations for therapeutic or diagnostic purposes, because as suggested by both Allen and Wallach, the liposomes can contain a contrast agent."

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Layla Soroush whose telephone number is (571)272-5008. The examiner can normally be reached on 8:30a.m.-5:00p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571)272-

0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER

Continuation of Disposition of Claims: Claims rejected are 100,102,127,194-200,203,210-213,217-228,294-300,303,310-329,331-337,347-356 and 412.